

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052867 A1

(51) International Patent Classification⁷: **C07D 239/42**,
C07F 9/535, 7/18

(74) Common Representative: **RANBAXY LABORA-**
TORIES LIMITED; c/o Deshmukh, Jayadeep R., 600
College Road East, Princeton, NJ 08540 (US).

(21) International Application Number:
PCT/IB2002/005213

(22) International Filing Date:
10 December 2002 (10.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **RAN-**
BAXY LABORATORIES LIMITED [IN/IN]; Nehru
Place 19, 110 019 New Dehli (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KUMAR, Yaten-**
dra [IN/IN]; U-26/5, Phase - III, DLF Qutab Enclave,
Haryana, 122001 Gurgaon (IN). **MEERAN, Hashim,**
Nizar, Poovanathil, Nagoor [IN/IN]; Uzhijethu House,
Vettipuram, P.O. Pathanamithitta, 689645 Kerala (IN). **DE,**
Shantanu [IN/IN]; G-1220, Chitranjan Park, 110019 New
Delhi (IN). **RAFEEQ, Mohammad** [IN/IN]; Harrai Pur
(Amria), Pilibhit, 262121 Uttar Pradesh (IN). **SATHYA-**
NARAYANA, Swargam [IN/IN]; H. No. 9-6-96/2, Ram
Nager, Karim Nager, 505 002 Andhra Pradesh (IN).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 2004/052867 A1

(54) Title: PROCESS FOR THE PREPARATION OF ROSUVASTATIN

(57) Abstract: The present invention relates to a process for the preparation of rosuvastatin calcium, a promising new HMG-CoA reductase inhibitor.

PROCESS FOR THE PREPARATION OF ROSUVASTATIN

FIELD OF THE INVENTION

The present invention relates to a process for the preparation rosuvastatin, a promising new HMG-CoA reductase inhibitor.

5

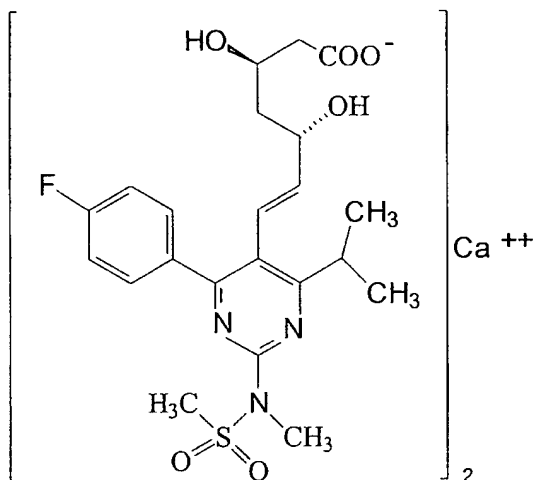
BACKGROUND OF THE INVENTION

HMG-CoA reductase inhibitors, popularly known as statins, are among the most widely prescribed lipid – lowering drugs.

Chemically rosuvastatin is (+)-(3R,5S)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]3,5-dihydroxy-6(E)-heptenoic acid
10 calcium salt (2:1) having the structural formula I.

15

20



25

FORMULA I

Rosuvastatin is an antihypercholesterolemic drug used in the treatment of atherosclerosis.

Hypercholesterolemia is now well recognized as a primary risk in coronary heart disease. Clinical studies with lipid lowering agents have established that
30 decreasing elevated serum cholesterol level reduces the incidence of cardiovascular

mortality. Recently, it has been found that rosuvastatin calcium has consistently shown greater potency than other currently marketed statins (atorvastatin, simvastatin and pravastatin) in preclinical and clinical testing.

Rosuvastatin and a process for its preparation is disclosed in U.S. Patent No. 5,260,440. The process disclosed therein involves four distinct chemical steps: (1) condensation of methyl (3R)-3-[(*tert*-butyldimethylsilyl) oxy]-5-oxo-6-triphenylphosphoranylidene hexanoate with 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarboxaldehyde; (2) deprotection of the 3-hydroxyl group to give the keto alcohol; (3) reduction of 5-oxo to get the chiral dihydroxy heptenoate; and (4) hydrolysis of the dihydroxy heptenoate.

The generation of the phosphorane side chain requires eight synthetic steps and involves expensive reagents. The process is both uneconomical and time consuming, hence not suitable for commercial production.

It is, therefore, desirable to provide an efficient process for the preparation of rosuvastatin which improves the economics by employing less expensive reagents and is more productive.

SUMMARY OF THE INVENTION

The present invention provides a process and novel intermediates for the preparation of rosuvastatin, its salts, esters, or the corresponding cyclized lactone form. The process provides obvious benefits with respect to economics and convenience to operate on a commercial scale.

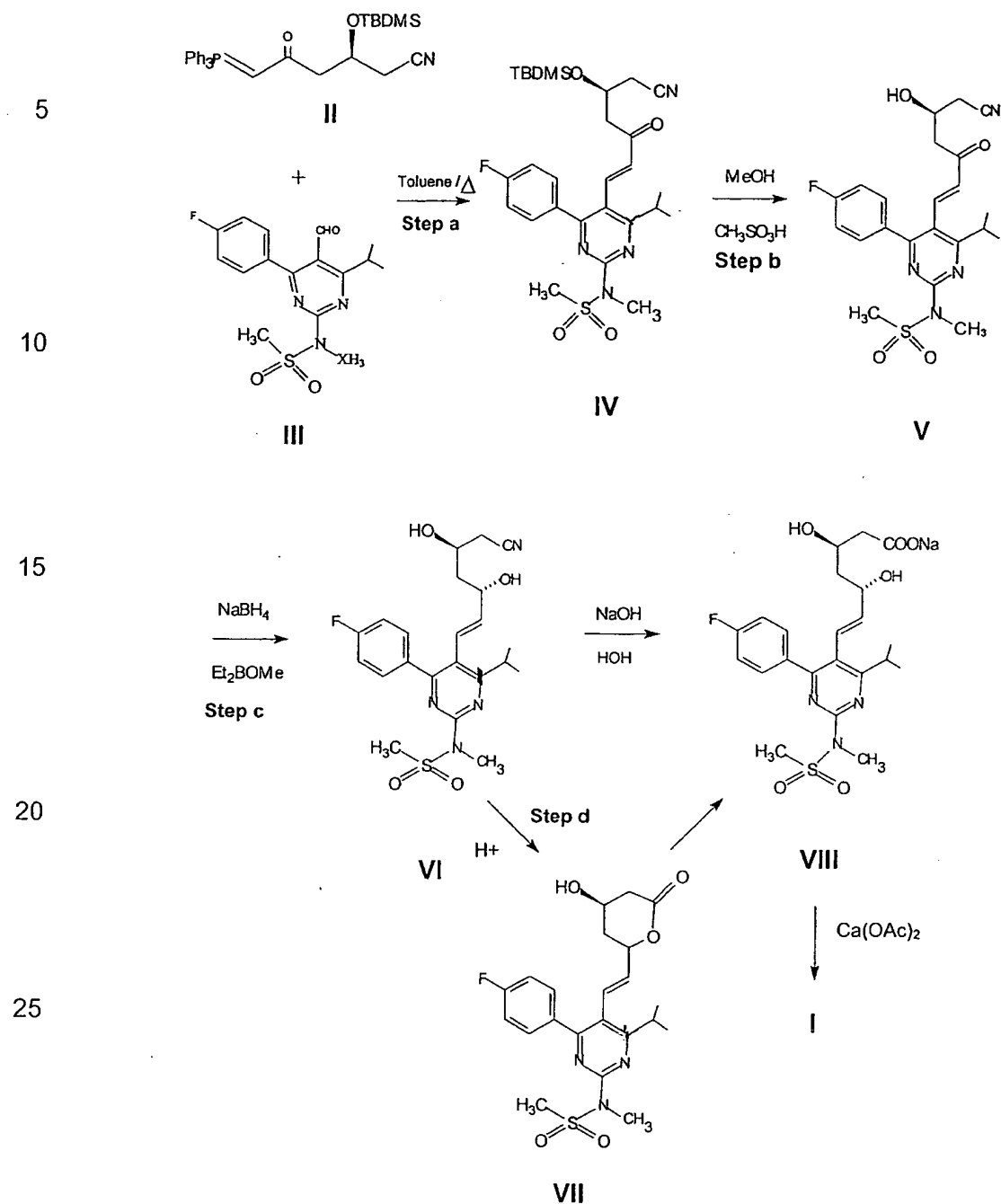
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of rosuvastatin of structural formula I as shown in Scheme I or the corresponding ring closed lactone form, comprising:

- (a) condensing 1-cyano(2S)-2-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III to give a condensed product of structural formula IV,

- 5
- (b) deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V,
 - (c) reducing the cyanoketo alcohol to cyanodiol of structural formula VI, and
 - (d) hydrolyzing the cyanodiol of structural formula VI to produce said compound of structural formula I in free acid form, or in the form of an ester or a lactone thereof, or in salt form.

Scheme I



The condensation at step (a) is performed in the presence of an organic solvent, especially such as toluene, benzene, cyclohexane, heptanes, acetonitrile, tetrahydrofuran, dioxane and ethyl acetate. The reaction is carried out for about 1 to about 100 hours.

The deprotection of the tert-butyldimethylsilyl group at step (b) is performed in an organic solvent in the presence of acids or tetrabutylammonium fluoride to give a cyanoketo alcohol of formula V.

5 The organic solvent is selected from solvents such as sulfolane, dioxane, dimethylsulfoxide, dimethylacetamide, N-methyl pyrrolidone, acetonitrile, diethyl ether, tetrahydrofuran, dimethylformamide, and lower alcohols such as methanol, ethanol, propanol.

10 The acids used for deprotection are selected from sulfonic acids such as methanesulfonic acid, trifluoromethane sulfonic acid, inorganic acids such as hydrochloric acid, sulfuric acid nitric acid, phosphoric acid and organic acids such as formic acid, trifluoroacetic acid, acetic acid.

15 The cyanoketo alcohol of formula V obtained in step (b) is reduced with diethylmethoxyborane and sodium borohydride. The reduction is performed in an organic solvent mixture comprising alcohols and non-alcoholic solvents. The reaction is worked up after completion to afford cyanodiol of formula VI.

The organic solvent mixture includes alcohols such as methanol, ethanol, propanol and butanol. The non-alcoholic organic solvent includes solvents such as acetonitrile, diethyl ether, tetrahydrofuran and dimethylformamide.

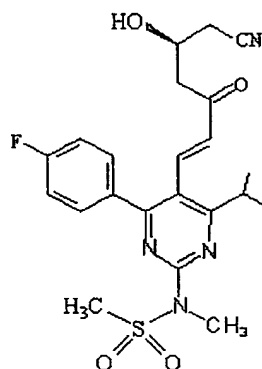
20 The reaction at step (c) is performed at a temperature from about -100°C to about 20°C, for example from about -80°C to about -70°C under cooling for about 10 minutes to about 20 hours, for example for about 30 minutes to about 10 hours.

25 The cyanodiol of formula VI is hydrolyzed by acids at step (d) to afford lactone of formula VII. Acids, which may be used, include inorganic acids such as hydrochloric acid, sulfuric acid and the like. The cyanodiol of Formula VI can be directly converted to its sodium salt of formula VIII.

The lactone obtained in step (d) is converted into its sodium salt of formula VIII and then to its hemicalcium salt of rosuvastatin of formula I by treatment with calcium acetate.

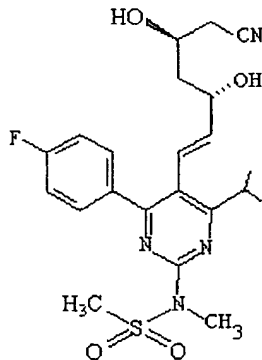
30 In another aspect of the invention, rosuvastatin is prepared by a process which comprises treatment of the condensed product of structural formula IV with an

alcohol, such as methanol, ethanol, propanol, and the like and an acid such as hydrochloric acid to provide an ester of formula IX



FORMULA IX

5 which is reduced to provide a compound of formula X,



FORMULA X

10 which in turn, is hydrolyzed to give rosuvastatin by the same method as described in steps (c) and (d) of Scheme I.

The starting material of formula III may be prepared, for example, as described in U.S. Patent No. 5,260,440.

The methods known in the art may be used with the process of this invention to enhance any aspect of the process. The product obtained may be further purified

by any technique known to a person skilled in the art, for example, crystallization, column chromatography, preparative high pressure liquid chromatography, preparative thin layer chromatography, extractive washing in solution or a combination of these procedures.

- 5 In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these are not intended to limit the scope of the present invention in any way.

EXAMPLES

- Preparation of rosuvastatin (+)-(3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1).
- 10

EXAMPLE 1

Step A

- Preparation of condensed product N-[5-[(tert-Butyl-dimethyl-silanyloxy)-6-cyano-3-oxo-hex-1-enyl]-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide (Condensed product, Formula IV)
- 15

- To a solution of pyrimidine aldehyde (1.0gm) of Formula III in toluene (20ml), 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of formula II was added and the reaction mixture was refluxed for about 20 24 hours. The reaction mixture was concentrated and the residue titrated with cyclohexane (50ml). The cyclohexane layer was concentrated to give a residue which was purified by silica gel chromatography, eluted with toluene to obtain 1.60gm of the condensed product as a thick oil.

Step B

- Preparation of cyanoketo alcohol-N-[5-(6-cyano-5-hydroxy-3-oxo-hex-1-enyl)-4-(4-fluoro-phenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide (Cyanoketo alcohol, Formula V)
- 25

- To a solution of the condensed product (1.0gm) in methanol (10ml), a solution of (0.8ml) of methanesulfonic acid in water (4.6% w/w) was added dropwise at 10-30 15°C. The reaction mixture was stirred for 24 hours at room temperature, concentrated and the residue was dissolved in methylene chloride (10ml). The solution was washed with 1% sodium bicarbonate followed by brine. The organic

layer was concentrated to give a residue which was purified by column chromatography over silica gel, eluted with toluene to give (0.65gm) cyanoketo alcohol as a solid.

Step C

5 **Preparation of cyanodiol N-[5-(6-cyano-3,5-dihydroxy-hex-1-enyl)-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide. (Cyanodiol, Formula VI)**

To a solution of the cyanoketo alcohol (1.0 g) in tetrahydrofuran (THF) (25ml), methanol (7ml) was added and the solution was cooled to -78°C . Diethylmethoxy
10 borane (2.3ml) in THF (1M) at -76°C to -78°C was added to the reaction mixture. The reaction mixture was stirred for 30 min and sodium borohydride (0.10gm) was added. The reaction mixture was further stirred at the same temperature for 3 hours and the temperature was allowed to rise to 25°C in 45 minutes. Acetic acid (1.4ml) was added and stirred for 10 min. The solvent was evaporated under vacuum and
15 then methanol (10ml) was added which was also evaporated off. Ethyl acetate (10ml) was added and the solution was washed with aqueous sodium bicarbonate solution (3ml). The organic layer was washed with brine (5ml) and then dried over sodium sulfate. The concentration of the solution under reduced pressure yielded cyanodiol as oil (0.8 gm).

20 **Step D**

Preparation of Rosuvastatin

Conc. HCl (2.5ml) was added to the cyanodiol (0.5gm) and the reaction mixture was stirred at room temperature for 12 hours. The resulting solution was diluted with water (2.5ml), cooled to 5°C and then neutralized with 1% aqueous
25 sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (10ml). The ethyl acetate layer was concentrated and the resulting residue was dissolved in toluene (10ml). The toluene solution was refluxed for 2 hours and the solvent was evaporated to give rosuvastatin lactone. Ethanol (7ml) was added to the residue and stirred for 60 min followed by the addition of 0.1N aqueous NaOH(11ml). Ethanol
30 was evaporated under vacuum, followed by the dropwise addition of a solution of calcium acetate. After stirring for 2 hours, the product was filtered, washed and dried to give rosuvastatin hemicalcium salt (0.26 g).

EXAMPLE 2

Preparation of rosuvastatin from methyl ester of Formula IX

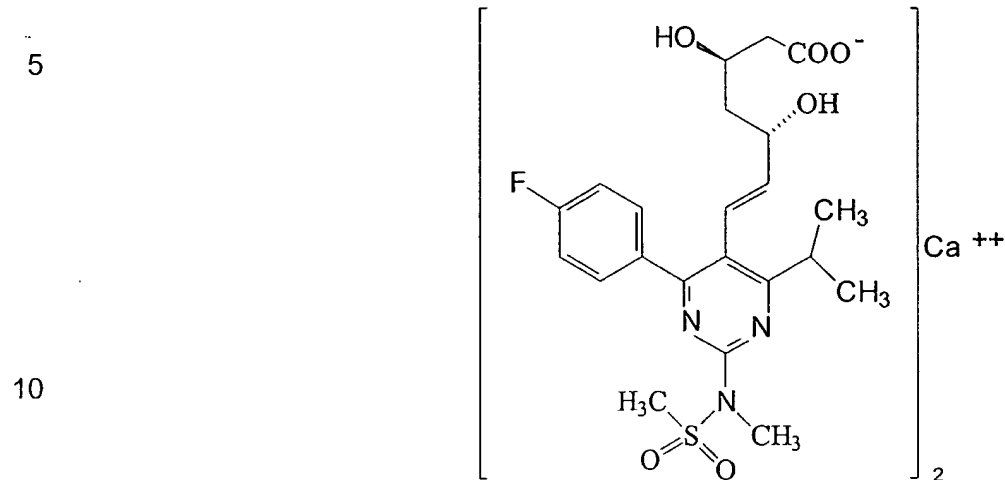
HCl gas was bubbled into a suspension of the condensed product (1.0 gm) of formula IV in methanol (10ml) at -40°C to -20°C for 2.5 hours. The resulting solution
5 was stirred at 0°C for 15 hours and then the solvent was removed. The residue was taken in ethyl acetate and washed with water (10ml). The pH of the organic layer was adjusted to 4.5 with aqueous sodium bicarbonate. The ethyl acetate layer was separated, washed with water and then with brine. The organic layer was concentrated to give a residue which was purified by column chromatography over
10 silica gel to give 0.8gm methyl ester of formula IX.

The methyl ester obtained above was reduced in the same way as described in step (c) of Example 1. Subsequent hydrolysis to the acid, its sodium salt formation and further conversion to the calcium salt was prepared as described in step (d) of Example 1 which afforded rosuvastatin hemicalcium salt (0.5g).

15 While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

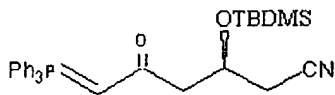
WE CLAIM:

1. A process for producing rosuvastatin of structural formula I,

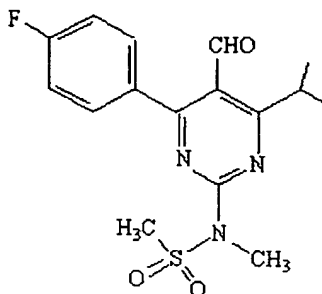
**FORMULA I**

comprising :

- a. condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of structural formula II

**FORMULA II**

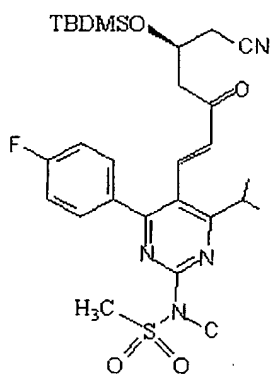
with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



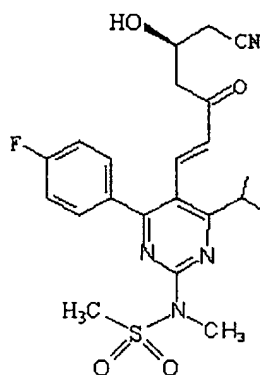
5

FORMULA III

to give a condensed product of structural Formula IV,

**FORMULA IV**

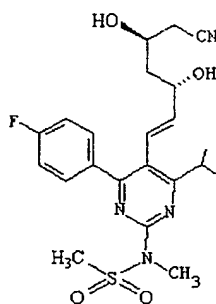
- b. deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V,



5

FORMULA V

- c. reducing the cyanoketo alcohol to cyanodiol of structural formula VI,
and

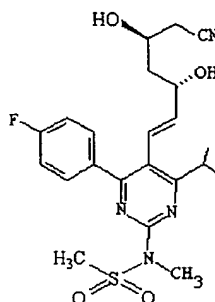


10

FORMULA VI

- d. hydrolyzing the cyanodiol of structural formula VI to produce said compound of structural formula I in free acid form, or in the form of an ester or lactone thereof, or in salt form.
2. The process of claim 1 wherein step (a) is carried out in an organic solvent.
- 5 3. The process of claim 2 wherein the organic solvent is selected from the group consisting of toluene, benzene, cyclohexanes, heptanes or mixture(s) thereof.
4. The process of claim 3 wherein the organic solvent is toluene.
5. The process of claim 1 wherein step (b) is performed in an organic solvent.
6. The process of claim 5 wherein the organic solvent is selected from the group
10 consisting of sulfolane, dioxane, dimethyl sulfoxide, dimethyl acetamide, N-methyl pyrrolidone, acetonitrile, diethyl ether, tetrahydrofuran, dimethylformamide, methanol, ethanol, propanol, and mixtures thereof.
7. The process of the claim 6 wherein the organic solvent is methanol.
8. The process of claim 1 wherein the deprotection at step (b) is performed by
15 treating with acids or tetrabutylammonium fluoride.
9. The process of claim 8 wherein the acids are sulfonic acids, inorganic or organic acids.
10. The process of claim 9 wherein the acids are selected from the group
20 consisting of methanesulfonic acid, trifluoromethanesulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, formic acid, trifluoroacetic acid, and acetic acid.
11. The process of claim 10 wherein the acid is methanesulfonic acid.
12. The process of claim 1 wherein the reduction at step c is carried out in the presence of diethylmethoxyborane and sodium borohydride.
- 25 13. The process of claim 12 wherein the reduction is performed in an organic solvent mixture comprising alcohol and non-alcoholic solvents.
14. The process of claim 13 wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol and butanol.
15. The process of claim 14 wherein the alcohol is methanol.

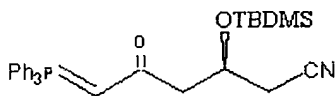
16. The process of claim 13 wherein the non-alcoholic organic solvent is selected from the group consisting of acetonitrile, diethyl ether, tetrahydrofuran and dimethylformamide.
17. The process of claim 16 wherein the non-alcoholic organic solvent is tetrahydrofuran.
18. The process of claim 1 wherein the hydrolysis at step (d) is performed after the reaction at step c is completed.
19. A process for preparing a compound of structural formula VI



FORMULA VI

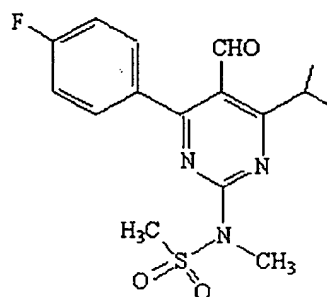
comprising:

- a. condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of structural formula II



FORMULA II

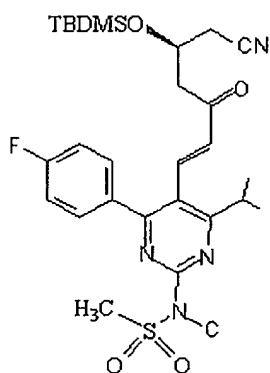
with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



5

FORMULA III

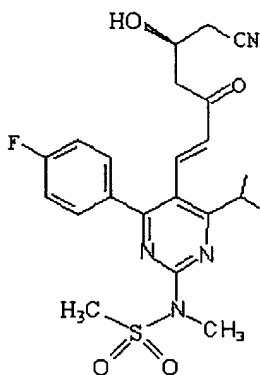
to give a condensed product of structural formula IV,



10

FORMULA IV

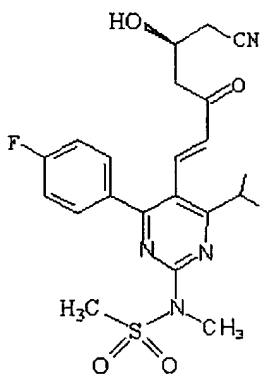
- b. deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V, and



5

FORMULA V

- (c) reducing the cyanoketo alcohol of structural formula V to produce said compound of structural formula VI.
20. A process for preparing a compound of structural formula V

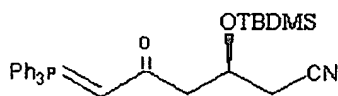


10

FORMULA V

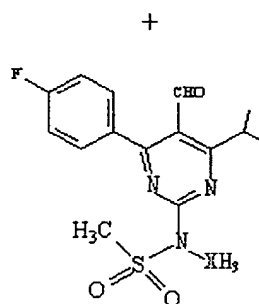
comprising:

- (a) condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of structural formula II



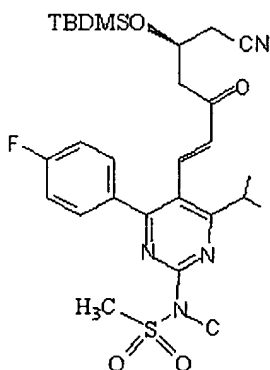
FORMULA II

- 5 with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



FORMULA III

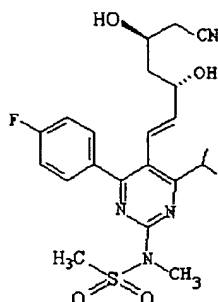
- 10 to give a condensed product of structural formula IV, and



FORMULA IV

- (b) deprotecting the tert-butyldimethylsilyl group of the condensed product to produce said compound of structural formula V.

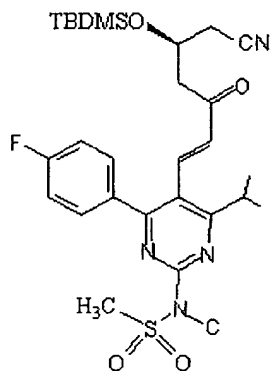
21. The process of claim 20 further comprising reducing the compound of structural formula V to produce a compound of structural formula VI.



5

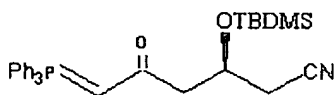
FORMULA VI

22. A process for preparing a compound of structural formula IV

**FORMULA IV**

comprising:

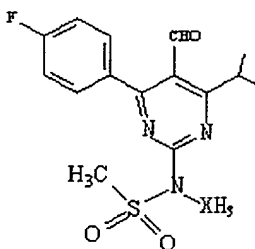
condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of structural formula II



5

FORMULA II

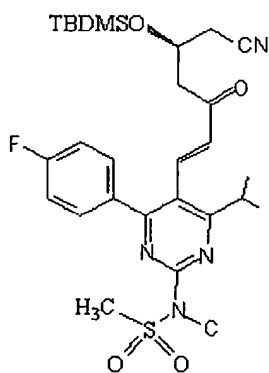
with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



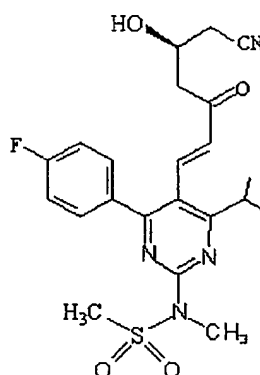
10

FORMULA III

to give a condensed product of structural formula IV.

**FORMULA IV**

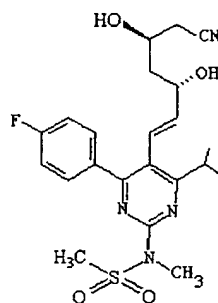
23. The process of claim 22 further comprising deprotecting the tert-butyl dimethylsilyl group of the condensed product to produce a compound of structural formula V.



5

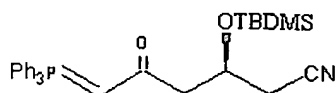
FORMULA V

24. The process of claim 23 further comprising reducing the compound of structural formula V to produce a compound of structural formula VI.

**FORMULA VI**

25. A process for producing rosuvastatin of structural formula I comprising:

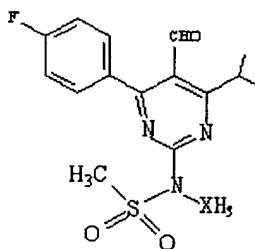
- (a) condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenylphosphanylidene hexanenitrile of structural formula II



5

FORMULA II

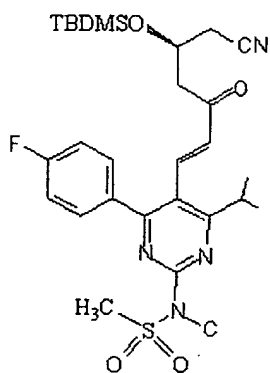
with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



10

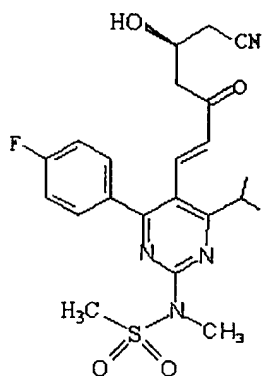
FORMULA III

to give a condensed product of structural formula IV,



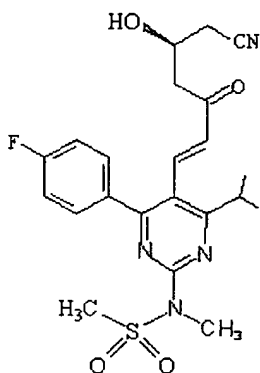
FORMULA IV

- (b) esterifying the condensed product to give an ester of a compound of structural formula IX,



FORMULA IX

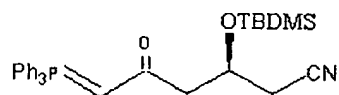
- 5 (c) reducing the ester to compound of structural formula X, and



Formula X

- (d) hydrolyzing the compound of structural formula X to produce said compound of structural formula I in free acid form, or in the form of an ester or a lactone thereof, or in salt form.
- 10
26. The process of claim 25 wherein step (a) is carried out in an organic solvent.
27. The process of claim 26 wherein the organic solvent is selected from the group consisting of toluene, benzene, cyclohexanes, heptanes or mixture(s) thereof.
- 15 28. The process of claim 27 wherein the organic solvent is toluene.

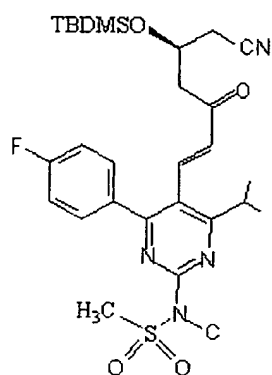
29. The process of claim 25 wherein step (b) is carried out with methanol in the presence of hydrochloric acid.
30. A compound of structural formula II.



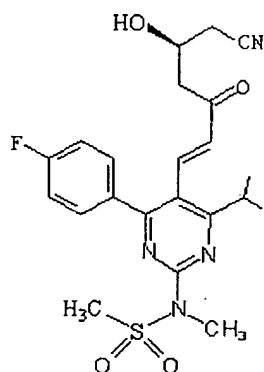
5

Formula II

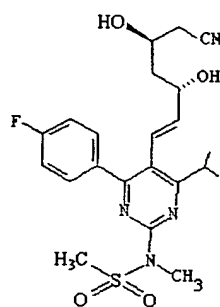
31. A compound of structural formula IV

**Formula IV**

- 10 32. A compound of structural formula V

**Formula V**

33. A compound of structural formula VI



Formula VI

INTERNATIONAL SEARCH REPORT

In nal Application No
F... B 02/05213

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D239/42 C07F9/535 C07F7/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D C07F		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) CHEM ABS Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 521 471 A (SHIONOGI) 7 January 1993 (1993-01-07) cited in the application page 1 -page 3; claims; examples 1-6 -----	1, 30-33
<div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">19 March 2003</div>		Date of mailing of the international search report <div style="text-align: center;">27/03/2003</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Francois, J</div>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/05213

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 521471	A	07-01-1993	AT 197149 T	15-11-2000
			CA 2072945 A1	02-01-1993
			DE 69231530 D1	30-11-2000
			DE 69231530 T2	13-06-2001
			DK 521471 T3	05-02-2001
			EP 0521471 A1	07-01-1993
			ES 2153824 T3	16-03-2001
			GR 3035189 T3	30-04-2001
			HK 1011986 A1	13-07-2001
			HU 220624 B1	28-03-2002
			HU 61531 A2	28-01-1993
			JP 2648897 B2	03-09-1997
			JP 5178841 A	20-07-1993
			KR 9605951 B1	06-05-1996
			PT 521471 T	30-04-2001
			US RE37314 E1	07-08-2001
			US 5260440 A	09-11-1993